DR. NICOLAS BARROS (Orcid ID : 0000-0002-8531-3537)
DR. JONATHAN A FRIDELL (Orcid ID : 0000-0002-8708-1506)

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Rabbit anti-thymocyte globulin administration to treat rejection in simultaneous pancreas and kidney transplant recipients with recent COVID-19 infection

Nicolas Barros[1], Asif A Sharfuddin[2],John Powelson[3], Muhammad Yaqub[2], Oluwafisayo O Adebiyi[2],Cole Beeler[1], Andrew Lutz[3], Jonathan A Fridell[3]

1. Department of Medicine, Division of Infectious Diseases, Indiana University School of Medicine
2. Department of Medicine, Division of Nephrology, Indiana University School of Medicine
3. Department of Surgery, Division of Transplantation, Indiana University School of Medicine

Corresponding author:
Nicolas Barros, MD
Indiana University School of Medicine
Assistant Professor of Clinical Medicine
Medical Director, Transplant Infectious Diseases
Indiana University Health, University Hospital
550 University Boulevard
Indianapolis, IN 46205
nbarros@iu.edu

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Transplant recipients may be more susceptible to COVID-19 and itsrelated complications.[1-3]Despite most patients being managed with reduction of immunosuppression, the risk of rejection or graft loss does not seem to be increased during COVID-19.[1,2,4,5]

The use of lymphocyte depleting agents has the inherent potential of impairing lymphocyte responses that are required for viral control.[6,7] However, their use may be unavoidable in steroid-resistant rejection. We report the administration of rabbit anti-thymocyte globulin (rATG) for steroid-resistant acute allograft rejection in two recipients ofsimultaneous pancreas and kidney transplant (SPK) who recovered from COVID-19 but continued to have viral shedding.

A 53-year-old female who underwent SPK on 02/08/2019diagnosed with mild COVID-19 on06/06/2020without requiringreduction of immunosuppressionwas admitted on 06/26/2020 with presumed pancreas allograft rejection due to elevated lipase levels(baseline 4 units/L, on admission 691 units/L) and fat stranding surrounding both kidney and pancreas allograft on imaging. SARS-CoV-2 PCR and IgG were positive. Despite treatment with high-dose steroids she had rising lipase and worsening enhancement of the pancreas allograft. Given presumed steroid-resistant rejection, she received empiric therapy withrATG(total 7.5 mg/kg) with subsequent normalization of lipase levels. Clinically, she recovered well without any signs or symptoms of recurrent COVID-19 (Table 1).

A 46-year-old male who underwent SPK on 01/21/2017, who was diagnosed with asymptomatic COVID-19 on 05/12/2020after his wife tested positive for COVID-19, was admitted on 07/01/2020 for management of biopsy proven acute cellular rejection and chronic active antibody-mediated rejection with new donor-specific antibodies.His creatinine had increased from baseline 1.3 mg/dL to 8.4 mg/dL. Repeat SARS-CoV-2 PCR and IgG were positive. He underwent plasma exchange,rituximab, IVIGand rATG (total 5 mg/kg). Following plasma exchange he experienced sero-reversion of SARS-CoV-2 IgG. While his renal function did not respond to therapy, hedidnot experience any signs or symptoms of COVID-19. (Table 2)

Neither of our patients had reduction of their immunosuppression and had stable drug levels, suggesting that compliance was not associated with the development of rejection. Although speculative, the profound inflammatory response during COVID-19 could potentially be a cause of

the rejection. While steroids can lead to prolonged viral shedding, the use of steroids has been shown to reduce mortality in hospitalized patients with severe COVID-19.[8,9]

Our patients continued to have viral shedding when rejection was diagnosed. Viral shedding has been detected up to 119days from symptom initiation and prolonged shedding is not a rare phenomenon[10]. However, the duration of infectivity remains unknown.[11]Several studies have correlated results from PCR and viral cultures. Three different authors independently reported positive cultures up to 8 days, while two others havereported positive cultures up to 18 and 20 days.[12-1415,16] A heart transplant recipient with mild COVID-19 3 months after his transplantation, had positive viral cultures up to 21 days, while his PCR remained positive up to 35 days.[18] Recently, a patient with lymphoma and associated B-cell immunodeficiency developed chronic symptomatic COVID-19 was found to have positive viral cultures for at least 119 days. The lack of seroconversion suggested an important role of humoral responses for the control of SARS-CoV-2. [10]

While the current guidelines generally recommend against initiation or augmentations of immunosuppression while patients have ongoing SARS-CoV-2 PCR positivity, our patients did not experience any signs or symptoms of recurrent COVID-19 suggesting that PCR positivity does not necessarily indicate infectivity. However, the management of rejection in patients with recent COVID-19 and positive SARS-CoV-2 PCR should be individualized.This is particularly useful in the setting of heart, lung and liver transplants.

Disclosure

The authors of this manuscript have no conflicts of interestto disclose as described by Clinical Transplantation.

Contributions:

Barros N, Sharfuddin A, Friedel J: Drafting article

Powelson J, Yaqub M, Adebiyi O,Beeler C, Lutz A: Critical revision of article

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Table 1. Timeline of testing and clinical data from patient 1

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	Day 0	Day 3	Day 6	Day 23 (First admission)	Day 26	Day 30,31,32	Day 33 (Discharge day)	Day 36 (Sedond admission) **rATG given**	Day 47	Day 57	Day 78
COVID-19 data											
SARS-CoV-2 PCR	Positive	Positive	Positive	Positive		Inconclusive		Positive	Negative		
SARS-CoV-2 IgG antibody					Detected				Detected		
Clinical data											
Lipase				571 U/L			1067 U/L	1780 U/L	805 U/L	335 U/L	24 U/L
C-peptide								3.8 ng/mL	6.7 ng/mL	2.7 ng/mL	2.3 ng/mL
Hemoglobin A1C				5.4%				6.1%	6.7%	6.5%	
DSA						Negative			Negative		

Table 2. Timeline of testing and clinical data from patient 2

	Day 0	Day 46	Day 48 (First admission)	Day 50, 51	Day 55	Day 56-62 **rATG given**	Day 63	Day 75 (Second admission)	Day 77
COVID-19 data									
SARS-CoV-2 PCR	Positive		Positive		Positive				
SARS-CoV-2 IgG antibody				Detected			Negative	Negative	
Clinical data									
Creatinine		8.4 mg/dl		9.5 mg/dl	10.4 mg/dl	9-10 mg/dl		8.6 mg/dl	
Other clinical data		Tacrolimus 5.1 ng/ml		DSA positive *	Hemoglobin A1C: 6.5%	Total plasma exchange	Hemoglobin A1C: 6.8%	HD started on day 76	DSA positive **
		Sirolimus 2.9 ng/mL		Stent placement		on days 56,57,59, 61, 61		Lipase: 75 U/L	
		Lipase 156 U/L				IVIG		C-peptide: 6.5 ng/mL	
		C-peptide: 1.9 ng/mL				rATG			
						Rituximab			

*DSA Pre-Treatment (Day 50) A2 5200; B51 2900, DR 1 5800, DR9 10100, DR 53 12200, DQ9 13300

** DSA 27 days post-Treatment (Day 77) A2 800, DR1 900, DR 9 5000, DR53 23500, DQ9 22600.